REMARKS

In response to the Office Action of February 20, 2009, Applicants have amended claim 21 to recite that the claimed attenuated live parasite comprises a ribosomal protein gene of said parasite, which is under the control of an inducible promoter, by which the promoter can be switched on and off, regulating the expression of the ribosomal protein gene to limit ribosome synthesis, which limits parasite replication in infected cells. This amendment is made for purposes of clarification. The gene is a ribosomal protein gene of the parasite and not a heterologous gene.

The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. § 103(a) for being obvious over Titus et al in view of Yan et al. has been maintained. Titus et al is relied on for teaching the development of a safe, live, attenuated *Leishmania* vaccine by gene replacement, although Titus et al do not teach *Leishmania* comprising a ribosomal protein gene under the control of an inducible promoter. Yan et al is relied for teaching tetracycline regulated gene expression in *Leishmania* with an inducible system that provides stringent regulation of gene expression..

The rejection of claims 21, 28-32 and 34-35 over Titus et al in view of Yan et al is respectfully traversed. The present claims, as now amended, are directed to an attenuated, live parasite wherein a ribosomal protein gene of the parasite is under the control of an inducible promoter, the promoter being able to be switched on or off, which regulates the expression of ribosomal protein genes, whereby ribosome synthesis is limited, thereby limiting parasite replication in infected cells. The result of limiting ribosome synthesis, and therefore the replication of the parasite itself after infecting cells, is not suggested in the prior art. The ordinary practitioner would find no suggestion in the prior art to prepare the modified parasite as presently claimed.

Yan et al. describe a Leishmania construct wherein a Tet responsive element can be inserted into different locations of the Leishmania genome, and the regulated expression of the

heterologous gene insert.. They teach the insertion of the expression construct into the tubulin gene region or the vicinity of the ribosomal RNA genes. It is never inserted near the ribosomal protein genes, as in the present invention, and, most importantly, there is no intention of regulating ribosomal protein genes, or any other genes, of the parasite itself. Yan et al. direct their attention to finding efficient insertion sites for expression heterologous genes. Ribosomal RNA genes and ribosomal protein genes are different and fulfill different functions in the lifecycle of the parasite. Moreover, there is no suggestion of limiting replication after infection to achieve attenuation by regulating the function of the ribosomal protein gene in any of the cited art.

Claims 21, 28-32 and 34-35 stand rejected under 35 U.S.C. § 102(b) for anticipation by Wirtz et al. It has been asserted that Wirtz et al teach the inducible expression system for T. brucei that allows precise control of expression of genes through a range of four orders of magnitude. The Examiner relies on Wirtz et al. for teaching inducible expression systems, "heterologous expression based inducible systems..."

The rejection over Wirtz et al is respectfully traversed. Applicants respectfully submit that Wirtz et al did not teach the regulation of expression by controlling expression of ribosomal protein genes of the parasite, but, instead, the regulation of expression by regulating expression of inserted heterologous genes. "[T]he system is based on the import into T. brucei of the regulatory elements of the tetracycline resistance operon (3) of Escherichia coli." (page 1180, col.1, lines 9-12). Although the heterologous gene may be inserted in the vicinity of the ribosomal RNA genes they are not themselves regulated. More importantly, perhaps, the ribosomal genes mentioned code for ribosomal RNA, they are not translated to encode any ribosomal proteins. In the *Leishmania* gene genome of Wirtz et al, the ribosomal protein genes are located in a different section of the genome from that wherein the heterologous genes are inserted. Consequently, there is no regulation of a ribosomal protein gene suggested by Wirtz et al. and no regulation of expression of the parasite's own genome or the attenuation of the parasite thereby. In fact, with the object being the expression of a heterologous gene, the result of which

affects the pathogenicity of the parasite, Wirtz et al. would not seek the limitation of expression of the gene under the control of the promoter, as in the present invention.

Claims 21-29 and 33-35 stand rejected under 35 USC 103(a) for bein obvious over Sutherland et al. taken with Durocher and Gozar et al.

The rejection over Southerland et al. taken with Durocher and Gozar et al. is respectfully traversed. As acknowledged by the Examiner, Southerland et al. merely teach protection against challenge afforded by attenuated organisms, nothing about ribosomal protein gene expression under the control of an inducible promoter, or the consequent reduction in replication of an organism. Similarly, Durocher fails to suggest controlling expression of a parasite's ribosomal protein gene to limit replication after infection and thereby attenuate a parasite. Gozar et al. report on a study of an RNA gene, not a protein gene. The product of RNA gene expression is RNA, not a protein. There is nothing to induce the practitioner to combine these references, and even if combined, they fail to suggest the invention presently claimed.

In view of the above, with the present amendment to 21, it is believed that claims 21-35, all claims in the application, are in condition for allowance.

Should the Examiner believe that a conference would be helpful in advancing the prosecution of this application, she is invited to telephone Applicants' attorney at the number below.

Applicants do not believe that any other fee is due in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **02-2334**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **02-2334**.

Respectfully submitted,

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